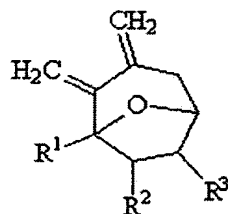


# SYNTHESIS OF 7-MEMBERED CARBOCYCLIC COMPOUND HAVING DIEXOMETHYLENE GROUPS

## BACKGROUND OF THE INVENTION

### 5 Field of the Invention

The present invention relates to a synthesis of a 7-membered carbocarbocyclic compound having diexomethylene groups, more particularly to a synthesis of a 7-membered carbocyclic compound having diexomethylene groups, a novel compound having the structure represented by the following Chemical Formula 1, from trimethylsilanylmethyl-allenol derivative by the intramolecular Prins cyclization using  
10 Lewis acid. The 7-membered cyclic compound is a useful intermediate for synthesis of other multicyclic compounds.



(I)

15 In Chemical Formula 1, R<sup>1</sup> is a C<sub>1</sub> to C<sub>6</sub> alkyl group, and R<sup>2</sup> and R<sup>3</sup> is respectively a hydrogen atom, or R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> may be connected with neighboring substituents to form a 5 to 10-membered aliphatic or aromatic ring.

## Description of the Related Art

7-membered carbocyclic compounds are important ingredients of biologically active natural substances and medicines. Recently, they are gaining interest in genetics because they are known to take part in cell division. For example, colchicine, which is known to be effective in treating gout [*J. Org. Chem.* 1985, **50**, 3425-3427], is a tricyclic compound having a 7-membered ring. According to a recent report, colchicine derivatives have high cell toxicity against general cancer cells and their resistant MDRs.

Since 7-membered carbocyclic compounds have good biological activity, development of a 7-membered carbocyclic compound with a new structure is a prerequisite for drug researches.

A cyclic compound having diexomethylene groups can be expanded to other multicyclic compounds through Diels-Alder reactions. Therefore, the compound represented by Chemical Formula 1, which has diexomethylene groups, is a very useful intermediate in synthesizing a multicyclic compound via Diels-Alder reactions.

## SUMMARY OF THE INVENTION

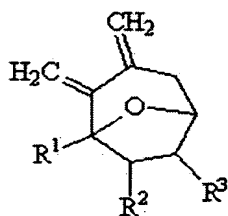
It is an object of the present invention to provide a 7-membered carbocyclic compound having diexomethylene groups, which is represented by Chemical Formula.

It is another object of the present invention to provide a method for synthesizing the novel compound represented by Chemical Formula 1 from a

trimethylsilanylmethyl-allenol derivative by the intramolecular Prins cyclization using Lewis acid.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

5           The present invention is characterized by a 7-membered carbocyclic compound having a new structure, which is represented by the following Chemical Formula 1:



(I)

10           In Chemical Formula 1, R<sup>1</sup> is a C<sub>1</sub> to C<sub>6</sub> alkyl group, and R<sup>2</sup> and R<sup>3</sup> is respectively a hydrogen atom, or R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> may be connected with neighboring substituents to form a 5 to 10-membered aliphatic or aromatic ring.

Also, the present invention is characterized by a method of synthesizing the compound represented by Chemical Formula 1 from a trimethylsilanylmethyl-allenol derivative by the intramolecular Prins cyclization in the presence of Lewis acid.

15           Hereinafter, the present invention is described in more detail.

The 7-membered carbocyclic compound represented by Chemical Formula 1, which is provided by the present invention, is a novel compound having diexomethylene groups, and it can be used as an active ingredient of medicines, or

intermediate of synthesizing multicyclic compounds in the field of medicine and precise chemistry.

Specific examples of the compound provided by the present invention include:

a compound wherein  $R^1$  is a  $C_1$  to  $C_3$  alkyl group, and  $R^2$  and  $R^3$  is respectively a  
5 hydrogen atom;

a compound wherein  $R^1$  and  $R^2$  are connected with each other to form a 5 to 10-membered aliphatic or aromatic ring, and  $R^3$  is a hydrogen atom; and

a compound wherein  $R^2$  and  $R^3$  are connected with each other to form a 5 to 10-membered aliphatic or aromatic ring, and  $R^1$  is a hydrogen atom.

10 The present invention also provides a method of synthesizing the compound represented by Chemical Formula 1 from a trimethylsilanylmethyl-allenol derivative by the intramolecular Prins cyclization in the presence of Lewis acid.

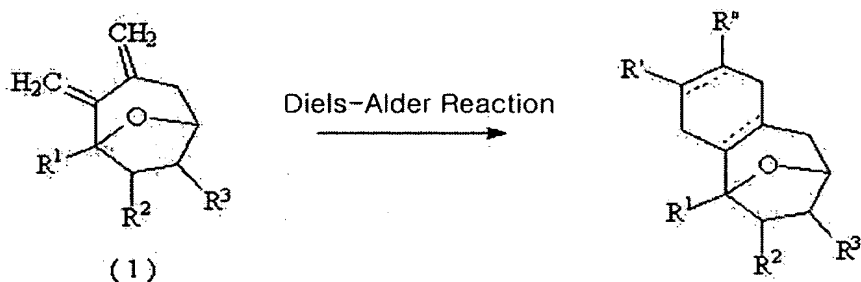
For the Lewis acid, such common Lewis acids as trimethylsilyl trifluoromethanesulfonate (TMSOTf) or indium halide ( $InX_3$ ,  $X = Cl$  or  $Br$ ) can be used.

15 Most preferably, TMSOTf is used. Preferably, the Lewis acid is used in 1.0 to 1.5 equivalent of the starting material, a trimethylsilanylmethyl-allenol derivative. For the reaction solvent, common organic solvents such as diethyl ether, tetrahydrofuran, dichloromethane, chloroform and ethyl acetate can be used. Most preferably, diethyl ether is used. The reaction is performed at from  $-90^\circ C$  to room  
20 temperature ( $25^\circ C$ ) for about 3 to 5 hours.

Since the aforementioned intramolecular Prins cyclization is industrially very

probable because it is relatively simple and offers good yield.

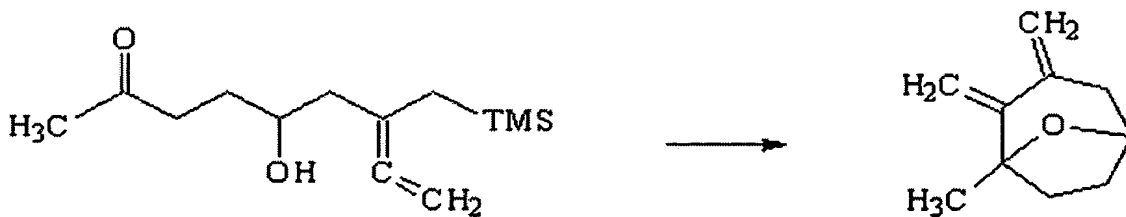
The compound represented by Chemical Formula 1 is useful in the field of medicine and precise chemistry. Because the compound represented by Chemical Formula 1 has diexomethylene groups, other multicyclic compounds can be prepared from it by Diels-Alder reactions.



Hereinafter, the present invention is described in more detail through Examples. However, the following Examples should not be construed as limiting the scope of the present invention.

## EXAMPLES

### Example 1: Synthesis of 1-methyl-2,3-dimethylene-8-oxa-bicyclo[3.2.1]octane

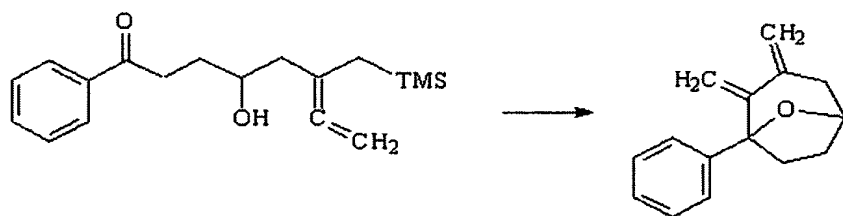


1.50 mL of diethyl ether was added to

5-hydroxy-7-trimethylsilanylmethyl-nona-7,8-diene-2-one (86 mg, 0.36 mmol) under nitrogen atmosphere. While stirring at  $-78^{\circ}\text{C}$ , trimethylsilyl trifluoromethanesulfonate (TMSOTf;  $64.7\ \mu\text{L}$ , 0.36 mmol) was added. While stirring the reaction mixture, the reaction temperature was slowly increased to room temperature for 3 hours. The reaction mixture was stirred at room temperature for 30 minutes. After the reaction was completed,  $\text{H}_2\text{O}$  was added. After stirring for about 5 minutes, the reaction mixture was diluted with ethyl acetate (EtOAc) and washed with water and saturated brine. The organic layer was separated from the reaction mixture and dried with anhydrous magnesium sulfate ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure and the remaining material was purified with column chromatography (EtOAc/*n*-hexane = 1/5) to obtain 51 mg of the product (94%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.17 (s, 1H), 5.29 (s, 1H), 4.78 (t, 2H,  $J = 5.6\ \text{Hz}$ ), 4.53 (s, 1H), 2.69 (d, 1H,  $J = 12.1\ \text{Hz}$ ), 2.36 (m, 2H), 1.85 (m, 3H), 1.51 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  152.51, 143.41, 112.19, 104.33, 81.86, 76.23, 42.42, 37.47, 30.22, 22.87 ppm.

### Example 2: Synthesis of 2,3-dimethylene-1-phenyl-8-oxa-bicyclo[3.2.1]octane

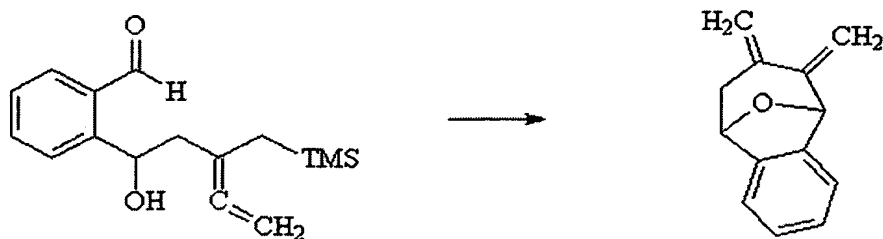


1.50 mL of diethyl ether was added to

4-hydroxy-1-phenyl-6-trimethylsilanylmethyl-octa-6,7-diene-1-one (110 mg, 0.36 mmol) under nitrogen atmosphere. While stirring at -78 °C, TMSOTf (64.7  $\mu$ L, 0.36 mmol) was added. While stirring the reaction mixture, the reaction temperature was slowly increased to room temperature for 3 hours. The reaction mixture was stirred at room temperature for 30 minutes. After the reaction was completed, H<sub>2</sub>O was added. After stirring for about 5 minutes, the reaction mixture was diluted with EtOAc and washed with water and saturated brine. The organic layer was separated from the reaction mixture and dried with anhydrous MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the remaining material was purified with column chromatography (EtOAc/*n*-hexane = 1/5) to obtain 74 mg of the product (96%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.33 (m, 5H), 5.20 (s, 1H), 4.94 (s, 1H), 4.87 (s, 1H), 4.74 (s, 1H), 3.99 (s, 1H), 2.84 (d, 1H, *J* = 17 Hz), 2.39 (t, 1H, *J* = 7.9 Hz), 2.29 (d, 1H, *J* = 14.2 Hz), 2.17 (m, 2H), 1.92 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  153.75, 143.58, 143.10, 128.06, 127.27, 127.00, 112.46, 108.18, 86.98, 76.04, 42.55, 37.17, 29.73 ppm.

**Example 3: Synthesis of 9,10-dimethylene-12-oxa-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2,3,5-triene**

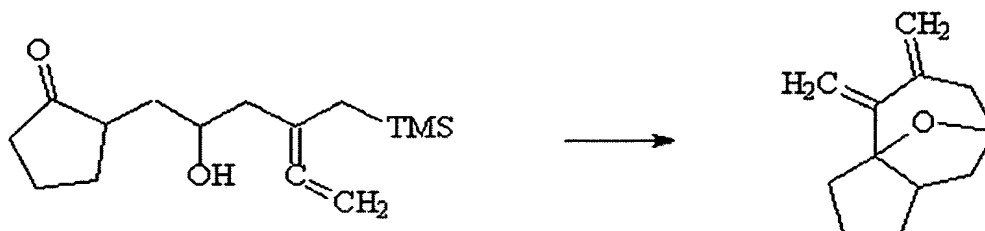


5.2 mL of diethyl ether was added to 2-(1-hydroxy-3-trimethylsilylmethyl-penta-3,4-dienyl)-benzaldehyde (358 mg, 1.30 mmol) under nitrogen atmosphere. While stirring at  $-78^{\circ}\text{C}$ , TMSOTf (235  $\mu\text{L}$ , 1.30 mmol) was added. While stirring the reaction mixture, the reaction temperature was slowly increased to room temperature for 3 hours. The reaction mixture was stirred at room temperature for 30 minutes. After the reaction was completed,  $\text{H}_2\text{O}$  was added. After stirring for about 5 minutes, the reaction mixture was diluted with EtOAc and washed with water and saturated brine. The organic layer was separated from the reaction mixture and dried with anhydrous  $\text{MgSO}_4$ . The solvent was removed under reduced pressure and the remaining material was purified with column chromatography (EtOAc/*n*-hexane = 1/6) to obtain 185 mg of the product (77%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.24 (m, 4H), 5.40 (s, 1H), 5.35 (d, 1H,  $J = 4.8$  Hz), 5.15 (s, 1H), 5.11 (s, 1H), 4.97 (s, 1H), 4.67 (s, 1H), 3.02 (br d, 1H,  $J = 15.0$  Hz), 2.37 (d, 1H,  $J = 14.4$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  146.20, 143.56, 143.01, 139.90, 127.68, 120.68, 114.16, 107.22, 83.31, 79.10, 38.56 ppm.



**Example 4: Synthesis of 9,10-dimethylene-11-oxa-tricyclo[5.3.1.0<sup>1,5</sup>]undecane**



1.1 mL of diethyl ether was added to

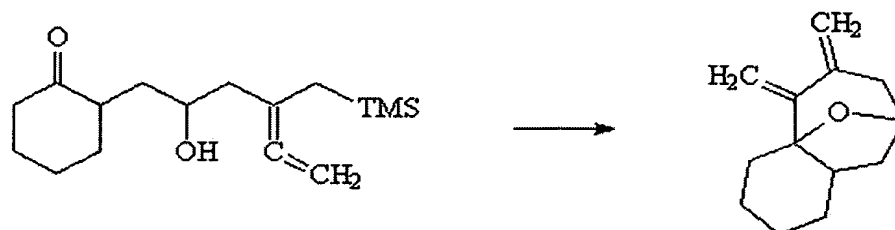
5 2-(2-hydroxy-4-trimethylsilylmethyl-hexa-4,5-dienyl)-cyclopentanone (70 mg, 0.26 mmol) under nitrogen atmosphere. While stirring at  $-78^{\circ}\text{C}$ , TMSOTf (48  $\mu\text{L}$ , 0.26 mmol) was added. While stirring the reaction mixture, the reaction temperature was slowly increased to room temperature for 3 hours. The reaction mixture was stirred at room temperature for 30 minutes. After the reaction was completed,  $\text{H}_2\text{O}$

10 was added. After stirring for about 5 minutes, the reaction mixture was diluted with EtOAc and washed with water and saturated brine. The organic layer was separated from the reaction mixture and dried with anhydrous  $\text{MgSO}_4$ . The solvent was removed under reduced pressure and the remaining material was purified with column chromatography (EtOAc/*n*-hexane = 1/15) to obtain 36 mg of the product

15 (77%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.17 (s, 1H), 5.04 (s, 1H), 4.81 (s, 2H), 4.58 (t, 1H,  $J = 6.3$  Hz), 2.73 (dd, 1H,  $J_1 = 14.6$  Hz,  $J_2 = 2.4$  Hz), 2.35 (m, 1H), 2.17 (m, 2H), 1.81 (m, 6H), 1.38 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  150.59, 144.25, 111.22, 103.66, 94.02, 77.70, 47.06, 41.53, 40.88, 34.60, 32.77, 25.02 ppm.

**Example 5: Synthesis of 10,11-dimethylene-12-oxa-tricyclo[6.3.1.0<sup>1,6</sup>]dodecane**



5            1.5        mL        of        diethyl        ether        was        added        to

2-(2-hydroxy-4-trimethylsilylmethyl-hexa-4,5-dienyl)-cyclohexanone (100 mg, 0.36 mmol) under nitrogen atmosphere. While stirring at -78 °C, TMSOTf (64.5  $\mu$ L, 0.36 mmol) was added. While stirring the reaction mixture, the reaction temperature was slowly increased to room temperature for 3 hours. The reaction mixture was

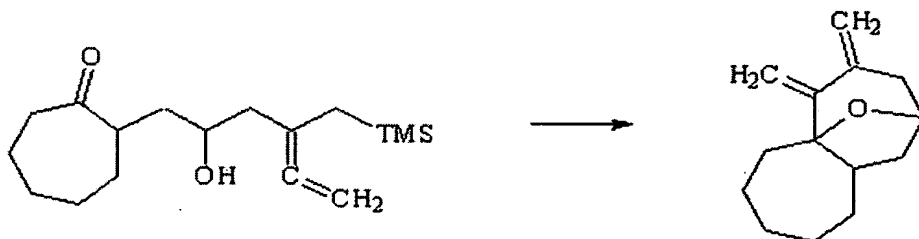
10 stirred at room temperature for 30 minutes. After the reaction was completed, H<sub>2</sub>O was added. After stirring for about 5 minutes, the reaction mixture was diluted with EtOAc and washed with water and saturated brine. The organic layer was separated from the reaction mixture and dried with anhydrous MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the remaining material was purified

15 with column chromatography (EtOAc/*n*-hexane = 1/6) to obtain 53 mg of the product (78%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.20 (s, 1H), 5.12 (s, 1H), 4.79 (s, 1H), 4.74 (s, 1H), 4.51 (s, 1H), 2.70 (d, 1H, *J* = 13.7 Hz), 2.15 (d, 1H, *J* = 14.3 Hz), 1.96 (m, 4H), 1.65 (m, 5H), 1.22 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  153.22, 143.83, 112.17, 106.14, 82.65, 73.73, 43.35,

42.09, 38.11, 31.43, 29.61, 23.21, 20.54 ppm.

**Example 6: Synthesis of 11,12-dimethylene-13-oxa-tricyclo[7.3.1.0<sup>1,7</sup>]tridecane**



5

1.30 mL of ether was added to 2-(2-hydroxy-4-trimethylsilylmethyl-hexa-4,5-dienyl)-cycloheptanone (95 mg, 0.32 mmol) under nitrogen atmosphere. While stirring at -78°C, TMSOTf (58.4  $\mu$ L, 0.32 mmol) was added. While stirring the reaction mixture, the reaction temperature was slowly increased to room temperature for 3 hours. The reaction mixture was stirred at room temperature for 30 minutes. After the reaction was completed, H<sub>2</sub>O was added. After stirring for about 5 minutes, the reaction mixture was diluted with EtOAc and washed with water and saturated brine. The organic layer was separated from the reaction mixture and dried with anhydrous MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the remaining material was purified with column chromatography (EtOAc/*n*-hexane = 1/6) to obtain 59 mg of the product (90%).

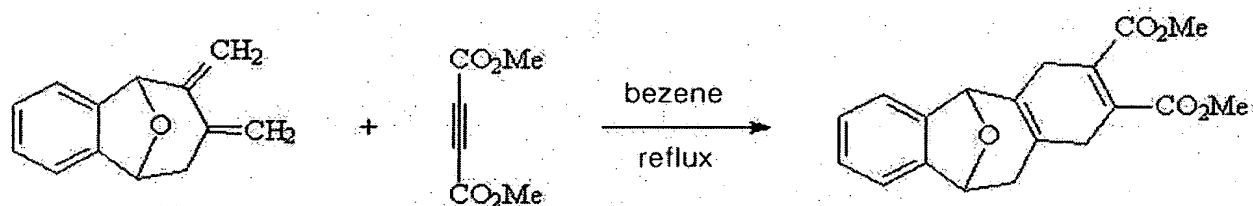
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  5.18 (s, 1H), 5.10 (s, 1H), 4.76 (s, 1H), 4.49 (s, 1H), 2.69 (d, 1H, *J* = 14.2 Hz), 2.14 (d, 1H, *J* = 14.4 Hz), 1.90 (m, 5H), 1.54 (m, 4H), 1.50 (m, 2H), 1.18

(m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  153.59, 144.90, 111.98, 105.15, 86.91, 75.53, 47.81, 42.55, 40.41, 34.63, 34.00, 31.98, 29.72, 25.08 ppm.

Comparative Example: Diels-Alder reaction using

5 **9,10-dimethylene-12-oxa-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2,3,5-triene**

The following is an example of synthesizing another multicyclic compound by Diels-Alder from the compound represented by Chemical Formula 1.



10            2.0 mL of benzene was added to 9,10-dimethylene-12-oxa-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2,3,5-triene (37 mg, 0.2 mmol) under nitrogen atmosphere. After adding dimethylacetylene dicarboxylate (85.62 mg, 0.6 mmol), the reaction mixture was stirred with reflux at 85°C for 5 hours. After the reaction was completed, H<sub>2</sub>O was added. After stirring for about 5 minutes, the reaction  
15 mixture was diluted with ethyl acetate and washed with water and saturated brine. The organic layer was separated from the reaction mixture and dried with anhydrous MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the remaining material was purified with column chromatography (EtOAc/*n*-hexane = 1/6) to obtain 39 mg of the product (60%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.17 (m, 4H), 5.42 (d, 1H,  $J = 5.97$  Hz), 4.92 (s, 1H), 3.77 (s, 1H), 3.73 (s, 1H), 2.84 (m, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  168.7, 147.7, 142.9, 133.6, 131.2, 130.4, 128.2, 127.4, 127.3, 121.4, 119.7, 117.8, 79.9, 78.8, 52.7, 32.9, 32.4, 28.9 ppm.

5 As described above, the present invention offers the following advantages:

1) Dimethylene cyclic compounds having a variety of structures can be synthesized using trimethylsilanylmethyl-alenol derivative as a starting material.

2) The synthesis reaction is simple.

3) The synthesis yield is high.

10 4) The diexomethylene cyclic compound is useful as an intermediate of synthesizing multicyclic compounds having a 7-membered ring, which are very important in the field of precise chemistry, by Diels-Alder reactions.

While the present invention has been described in detail with reference to the  
15 preferred embodiments, those skilled in the art will appreciate that various modifications and substitutions can be made thereto without departing from the spirit and scope of the present invention as set forth in the appended claims.